INTERNATIONAL SEARCH REPORT

Inte· 'ional Application No
PCI/EP 98/00497

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 96 39415 A (ISIS PHARMACEUTICALS INC ;CIBA GEIGY (CH); MONIA BRETT P (US); MAR) 12 December 1996	1-5, 7-11, 14-17
Y	see abstract see page 4, line 1 - line 27 see page 9, line 7 - page 14, line 6	4

X	YU D ET AL: "HYBRID OLIGONUCLEOTIDES: SYNTHESIS, BIOPHYSICAL PROPERTIES STABILITY STUDIES, AND BIOLOGICAL ACTIVITY" BIOORGANIC & MEDICINAL CHEMISTRY, vol. 4, no. 10, 1996, pages 1685-1692, XP000644792 see the whole document	1-5,7,8, 10,11, 15-17

X	ZHAO Q ET AL: "EFFECT OF DIFFERENT CHEMICALLY MODIFIED OLIGODEOXYNUCLEOTIDES ON IMMUNE STIMULATION" BIOCHEMICAL PHARMACOLOGY, vol. 51, no. 2, 26 January 1996, pages 173-182, XP000610208 see figures 2,3,5,6	1-5, 7-11,17

X	WO 95 00103 A (CHUNG HUN TAEG ;IL YANG PHARM CO LTD (KR)) 5 January 1995 see pages 6 and 7, SEQ IDs 1,4-8,10-21	1-4, 7-11, 14-17
A	see page 7, line 33 - page 10, line 12 see examples 4,5 see claims	13

X	JACHIMCZAK P ET AL: "TRANSFORMING GROWTH FACTOR-BETA-MEDIATED AUTOCRINE GROWTH REGULATION OF GLIOMAS AS DETECTED WITH PHOSPHOROTHIOATE ANTISENSE OLIGONUCLEOTIDES" INTERNATIONAL JOURNAL OF CANCER, vol. 65, no. 3, 26 January 1996, pages 332-337, XP000676566 see the whole document	1-4, 7-11, 13-17

X	HATZFELD J ET AL: "RELEASE OF EARLY HUMAN HEMATOPOIETIC PROGENITORS FROM QUIESCENCE BY ANTISENSE TRANSFORMING GROWTH FACTOR BETA1 OR RB OLIGONUCLEOTIDES" JOURNAL OF EXPERIMENTAL MEDICINE, vol. 174, no. 4, 1 October 1991, pages 925-929, XP002002256 cited in the application see the Rb and p53 antisenses	1-4,7-11

	-/--	

4

INTERNATIONAL SEARCH REPORT

Inte ional Application No
PCT/EP 98/00497

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 C12N15/11 C07H21/04 A61K31/70

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 C12N C07H A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X Y	WO 94 25588 A (BIOGNOSTIK GES FUER BIOMOLEKUL ;SCHLINGENSIEPEN GEORG FERDINAN (DE) 10 November 1994 see the whole document, and especially SEQ IDs : 1-56 and 137 for TGF-beta1, or SEQ IDs 57 and 136 for TGF-beta2 ---	1-16 4,6,12
X Y	WO 93 07883 A (ISIS PHARMACEUTICALS INC) 29 April 1993 see page 5, line 20 - page 7 see page 10, line 6 - page 12, line 7 see page 14, line 3 - line 20 see examples see page 59, line 27 - page 60 see claims --- -/--	1-4,6-12 6,12

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
5 November 1998	24.03.99

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	ANDRES S.M.

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

Int tional Application No
PCT/EP 98/00497

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	JACHIMCZAK, P. ET AL.: "The effect of transforming growth factor-beta2-specific phosphorothioate anti-sense oligodeoxynucleotides in reversing cellular immunosuppression in malignant glioma" J.NEUROSURGERY, vol. 78, 1993, pages 944-951, XP002083277 see the whole document	1-4, 7-11,13, 14,17
P,X	FITZPATRICK, D. ET AL.: "Antisense oligonucleotides specific for transforming growth factor beta2 inhibit the growth of malignant mesothelioma both in vitro and in vivo" CANCER RESEARCH., vol. 57, August 1997, pages 3200-3207, XP002083278 see the whole document	1-5, 7-11,13
A	AGRAWAL S: "Antisense oligonucleotides: towards clinical trials" TRENDS IN BIOTECHNOLOGY, vol. 14, no. 10, October 1996, page 376-387 XP004035728 see table 2 see page 379, left-hand column, line 39 - right-hand column, line 26 see page 383, right-hand column - page 384, right-hand column, paragraph 2	1-17
A	PISETSKY, D. & REICH, C.: "STIMULATION OF IN VITRO PROLIFERATION OF MURINE LYMPHOCYTES BY SYNTHETIC OLIGODEOXYNULEOTIDES" MOLECULAR BIOLOGY REPORT, vol. 18, no. 3, October 1993, pages 217-221, XP000610055 see the whole document	1-17
A	WO 95 02422 A (WELTMAN JOEL K) 26 January 1995 see the whole document	6,12
A	WO 96 31600 A (HYBRIDON INC) 10 October 1996 see the whole document	1-17
A	WO 90 10030 A (OLIN CORP) 7 September 1990 see page 4, line 20 - page 7, line 23 see claims	3-6, 10-12

4

Form PCT/ISA/210 (continuation of second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/EP 98/00497

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☐ Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

see additional sheet

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. ☒ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

inventions 1. and 39.01 (see continuation-sheet)

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☒ The additional search fees were accompanied by the applicant's protest.

☐ No protest accompanied the payment of additional search fees.

17

PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference	FOR FURTHER ACTION	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
980274wo Me/kk		
International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/EP98/00497	30/01/1998	31/01/1997

International Patent Classification (IPC) or national classification and IPC
C12N15/11

Applicant
BIOGNOSTIK GESELLSCHAFT FÜR BIOMOLEKULARE...et al.

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 5 sheets, including this cover sheet.

   ☐ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of sheets.

3. This report contains indications relating to the following items:

   - I ☒ Basis of the report
   - II ☐ Priority
   - III ☐ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - IV ☒ Lack of unity of invention
   - V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations suporting such statement
   - VI ☐ Certain documents cited
   - VII ☐ Certain defects in the international application
   - VIII ☐ Certain observations on the international application

Date of submission of the demand	Date of completion of this report
20/08/1998	08.07.99

Name and mailing address of the international preliminary examining authority:
European Patent Office
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Grosskopf, R

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Form PCT/IPEA/409 (cover sheet) (January 1994)

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/EP98/00497

I. Basis of the report

1. This report has been drawn on the basis of (*substitute sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to the report since they do not contain amendments.*):

Description, pages:

1-28 as originally filed

Claims, No.:

1-17 as originally filed

Drawings, sheets:

1/36-36/36 as originally filed

2. The amendments have resulted in the cancellation of:

- ☐ the description, pages:
- ☐ the claims, Nos.:
- ☐ the drawings, sheets:

3. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)):

4. Additional observations, if necessary:

IV. Lack of unity of invention

1. In response to the invitation to restrict or pay additional fees the applicant has:

- ☐ restricted the claims.
- ☐ paid additional fees.
- ☐ paid additional fees under protest.
- ☐ neither restricted nor paid additional fees.

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/EP98/00497

2. ☒ This Authority found that the requirement of unity of invention is not complied and chose, according to Rule 68.1, not to invite the applicant to restrict or pay additional fees.

3. This Authority considers that the requirement of unity of invention in accordance with Rules 13.1, 13.2 and 13.3 is

☐ complied with.

☒ not complied with for the following reasons:

see separate sheet

4. Consequently, the following parts of the international application were the subject of international preliminary examination in establishing this report:

☐ all parts.

☒ the parts relating to claims Nos. 1-17(partially).

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	
	No:	Claims	1-17
Inventive step (IS)	Yes:	Claims	
	No:	Claims	1-17
Industrial applicability (IA)	Yes:	Claims	1-17
	No:	Claims	

2. Citations and explanations

see separate sheet

Ad item IV:

This Authority agrees with the objection for lack of unity put forward by the search Authority.
The Applicant has paid one additional search fee and asked for an additional search of invention 39.01.
Consequently, also this Authority had to ask the Applicant to pay either an additional examination fee or to select one of the two groups searched.
However, taking into account the limited time period which is available for establishing the final report, this Authority will not insist on the payment of an additional examination fee, but will carry out an examination with regard to both groups.
This does, however, not mean that the lack of unity objection no longer applies.

Ad item V:

The following subject-matter has been searched and will, consequently, form the basis for this opinion:

(a) The method Claims 1 to 6
(b) the product claims insofar as they relate to the sequences of SEQ ID NO 41 and SEQ ID NO 519.

As far as the method claims are concerned and especially Claim 1, said method consists of two steps:

(i) the selection of a target sequence
(ii) the synthesis of an antisense oligonucleotide.

These two steps are "connected" by a rule which should be fulfilled by the resulting oligonucleotides. Said rule, however, has no consequences for the steps of preparing the oligonucleotides (otherwise one could also argue a method for preparing a compound having two C-atoms, i.e. the "rule" which must be fulfilled, is novel over a method for preparing acetic acid).
Thus, this rule has only relevance for the scope of the claim insofar as it has an

influence on the resulting products i.e. the oligonucleotides.
This means, however, if oligonucleotides which fall within the scope of said rule are known, the method for their preparation which consists merely of the two trivial steps mentioned above, could not be novel. Admittedly a method for preparing a known product may be novel, but merely if it comprises **steps** which do not form part of the prior art methods.
Since oligonucleotides are known which follow these rules (see e.g. D1; WO94/25588 but also several other documents cited in the search report), and said oligonucleotides are prepared by "selecting a target sequence" and "synthesising the oligonucleotide", at least Claims 1 and 2 are not novel.
The other features within Claims 3 to 6 (novelty provided, several of the alternatives mentioned in these claims would give rise to further objections for lack of unity) are routinely used as modifications during the preparation of antisense oligonucleotides (most of them also described in D1), and, thus, do not make any contribution to a possible inventive activity.

As far as the two products searched are concerned, they, strictly speaking, also lack novelty since they refer to sequences which "comprise" said sequences i.e. they encompass larger parts of the TGF-beta 1 and TGF-beta 2 gene.

But even if the claims were restricted to the specific fragments, an inventive activity could at best be acknowledged if said antisense oligonucleotides had some superior properties in comparison with antisense oligos which have been prepared or which could easily be prepared from the TGF genes, said oligos being even partially identical with these sequences (see e.g. SEQ ID NOs 57 and 136 of D1).
Such properties, however, have not been demonstrated e.g. by comparative tests.
Moreover, with regard to SEQ ID NO.: 519, it has to be mentioned that SEQ ID NO.: 57 of D1 is nearly **identical** (only one base shift). Thus, an inventive activity has to be denied in any case.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

INVENTION 1 : Claims 1-17 (all partially)
A method for preparing antisense oligonucleotides and antisenses obtained. Antisense oligonucleotide against the TGF-beta 1 gene and having SEQ ID 41, modified forms thereof, composition containing it and its therapeutic or diagnostic uses.

INVENTIONS 2 to 33 : Claims 1-17 (all partially)
As for subject 1, but concerning SEQ IDs 42 to 73 respectively (invention 2 concerns SEQ ID 42; invention 3, SEQ ID 43 ....; invention 33, SEQ ID 73).

INVENTION 34 : Claims 1-17 (all partially)
Antisense oligonucleotides against the p53 gene, modified forms thereof, composition containing them and their therapeutic or diagnostic uses.

INVENTION 35 : Claims 1-17 (all partially)
As for invention 34, but concerning the junB gene.

INVENTION 36 : Claims 1-17 (all partially)
As for invention 34, but concerning the junD gene.

INVENTION 37 : Claims 1-17 (all partially)
As for invention 34, but concerning the erbB-2 gene.

INVENTION 38 : Claims 1-17 (all partially)
As for invention 34, but concerning the c-fos gene.

INVENTION 39.01 : Claims 1-17 (all partially)
As for invention 34, but concerning the antisense oligonucleotide against TGF-beta 2 gene and having SEQ ID 519.

INVENTIONS 39.02 to 39.43 : Claims 1-17 (all partially)
As for invention 39.01, but concerning SEQ IDs 520 to 556 and 1273 to 1277 (invention 39.02 concerns SEQ ID 520; invention 39.03, SEQ ID 521.....; invention 39.38, SEQ ID 556; invention 39.39, SEQ ID 1273;...; and invention 39.43, SEQ ID 1277).

INVENTION 40 : Claims 1-17 (all partially)
As for invention 34, but concerning the Rb gene.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

INVENTION 41 : Claims 1-17 (all partially)
As for invention 34, but concerning the relA gene.

INVENTION 42 : Claims 1-17 (all partially)
As for invention 34, but concerning the p105/p50 gene.

INVENTION 43 : Claims 1-17 (all partially)
As for invention 34, but concerning the NFKB2 gene.

INVENTION 44 : Claims 1-17 (all partially)
As for invention 34, but concerning the TANK gene.

INVENTION 45 : Claims 1-17 (all partially)
As for invention 34, but concerning the I-kappa B epsilon gene.

INVENTION 46 : Claims 1-17 (all partially)
As for invention 34, but concerning the TRAF-6 gene.

INVENTION 47 : Claims 1-17 (all partially)
As for invention 34, but concerning the Rank gene.

INVENTION 48 : Claims 1-17 (all partially)
As for invention 34, but concerning the IL-5 gene.

INVENTION 49 : Claims 1-17 (all partially)
As for invention 34, but concerning the IL-13 gene.

INVENTION 50 : Claims 1-17 (all partially)
As for invention 34, but concerning the IL-15 gene.

INVENTION 51 : Claims 1-17 (all partially)
As for invention 34, but concerning the I-kappaB(new member) gene.

INVENTION 52 : Claims 1-17 (all partially)
As for invention 34, but concerning the Prostaglan.Rec.EP3 gene.

INVENTION 53 : Claims 1-17 (all partially)
As for invention 34, but concerning the Presenilin I gene.

INVENTION 54 : Claims 1-17 (all partially)
As for invention 34, but concerning the TRADD gene.

INVENTION 55 : Claims 1-17 (all partially)
As for invention 34, but concerning the PKA gene.

INVENTION 56 : Claims 1-17 (all partially)
As for invention 34, but concerning the IL-12 alpha gene.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

INVENTION 57 : Claims 1-17 (all partially)
As for invention 34, but concerning the IL-12 beta gene.

INVENTION 58 : Claims 1-17 (all partially)
As for invention 34, but concerning the Pg-R gene.

INVENTION 59 : Claims 1-17 (all partially)
As for invention 34, but concerning the thr gene.

INVENTION 60 : Claims 1-17 (all partially)
As for invention 34, but concerning the ref-fosjun gene.

INVENTION 61 : Claims 1-17 (all partially)
As for invention 34, but concerning the PIV gene.

INVENTION 62 : Claims 1-17 (all partially)
As for invention 34, but concerning the bak gene.

INVENTION 63 : Claims 1-17 (all partially)
As for invention 34, but concerning the bclx gene.

INVENTION 64 : Claims 1-17 (all partially)
As for invention 34, but concerning the bmp gene.

INVENTION 65 : Claims 1-17 (all partially)
As for invention 34, but concerning the ICE gene.

INVENTION 66 : Claims 1-17 (all partially)
As for invention 34, but concerning the ich gene.

INVENTION 67 : Claims 1-17 (all partially)
As for invention 34, but concerning the bcl1 gene.

INVENTION 68 : Claims 1-17 (all partially)
As for invention 34, but concerning the bcl2 gene.

INVENTION 69 : Claims 1-17 (all partially)
As for invention 34, but concerning the mucrep gene.

INVENTION 70 : Claims 1-17 (all partially)
As for invention 34, but concerning the AHR gene.

INVENTION 71 : Claims 1-17 (all partially)
As for invention 34, but concerning the CD2 gene.

INVENTION 72 : Claims 1-17 (all partially)
As for invention 34, but concerning the MEK2 gene.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

INVENTION 73 : Claims 1-17 (all partially)
As for invention 34, but concerning the TNF gene.

INVENTION 74 : Claims 1-17 (all partially)
As for invention 34, but concerning the TNFR gene.

INVENTION 75 : Claims 1-17 (all partially)
As for invention 34, but concerning the IL-18 gene.

INVENTION 76 : Claims 1-17 (all partially)
As for invention 34, but concerning an IL-12-rec gene.

INVENTION 77 : Claims 1-17 (all partially)
As for invention 34, but concerning the PKC-beta gene.

INVENTION 78 : Claims 1-17 (all partially)
As for invention 34, but concerning the CB-1-rec gene.

INVENTION 79 : Claims 1-17 (all partially)
As for invention 34, but concerning the TGF-alpha gene.

INVENTION 80 : Claims 1-17 (all partially)
As for invention 34, but concerning the Fascin gene.

INVENTION 81 : Claims 1-17 (all partially)
As for invention 34, but concerning the p300 gene.

INVENTION 82 : Claims 1-17 (all partially)
As for invention 34, but concerning the CBP gene.

INVENTION 83 : Claims 1-17 (all partially)
As for invention 34, but concerning the rac-alpha gene.

INVENTION 84 : Claims 1-17 (all partially)
As for invention 34, but concerning an EBV gene.

INVENTION 85 : Claims 1-17 (all partially)
As for invention 34, but concerning the HSPQ gene.

INVENTION 86 : Claims 1-17 (all partially)
As for invention 34, but concerning the CC-CKR1 gene.

INVENTION 87 : Claims 1-17 (all partially)
As for invention 34, but concerning the CC-CKR4 gene.

INVENTION 88 : Claims 1-17 (all partially)
As for invention 34, but concerning the c-CRK gene.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

INVENTION 89 : Claims 1-17 (all partially)
As for invention 34, but concerning the CRKL gene.

INTERNATIONAL SEARCH REPORT

Information on patent family members

Inte ional Application No
PCT/EP 98/00497

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9425588 A	10-11-1994	AU 6794594 A	21-11-1994
		EP 0695354 A	07-02-1996
		JP 8509370 T	08-10-1996
WO 9307883 A	29-04-1993	AU 2916292 A	21-05-1993
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		US 4885316 A	05-12-1989

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INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

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(34) Countries for which the regional or international application was filed: DE et al.

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(81) Designated States: AL, AU, BA, BB, BG, BR, CA, CN, CU, CZ, DE, EE, GE, GW. HU, ID, IL, IS, JP, KP, KR, LC, LK, LR, LT, LV, MG, MK, MN, MX, NO, NZ, PL, RO, SG, SI, SK, SL, TR, TT, UA, US, UZ, VN, YU, ARIPO patent (GH, GM, KE, LS, MW, SD, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG).

Published
With international search report.
Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.

(88) Date of publication of the international search report:
14 May 1999 (14.05.99)

(54) Title: AN ANTISENSE OLIGONUCLEOTIDE PREPARATION METHOD

(57) Abstract

A method for the preparation of an antisense oligonucleotide or derivative thereof comprising the steps of: selecting a target nucleic acid, if necessary elucidating its sequence; generating the antisense oligonucleotide with the proviso that: the oligonucleotide comprises at least 8 residues; the oligonucleotide comprises at maximum twelve elements, which are capable of forming three hydrogen bonds each to cytosine bases; the oligonucleotide does not contain four or more consecutive elements, capable of forming three hydrogen bonds each with four consecutive cytosine bases (CCCC) within the target molecule or alternatively four or more consecutive elements of GGGG; the oligonucleotide does also not contain 2 or more series of three consecutive elements, capable of forming three hydrogen bonds each with three consecutive cytosine bases (CCC) within the target molecule, or alternatively 2 or more series of three consecutive elements of GGG; and the ratio between residues forming two hydrogen bonds per residue (2H–bond–R) with the target molecule and those residues forming three hydrogen bonds per residue (3H–bond–R) with the target molecule, is ruled by the following specifications: 3H–bond–R/3H–bond–R + 2H–bond–R $\geq$ 0.29; and synthesizing the oligonucleotide thus generated in a per se known manner.

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INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

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Published
Without international search report and to be republished upon receipt of that report.

(54) Title: AN ANTISENSE OLIGONUCLEOTIDE PREPARATION METHOD

(57) Abstract

A method for the preparation of an antisense oligonucleotide or derivative thereof comprising the steps of: selecting a target nucleic acid, if necessary elucidating its sequence; generating the antisense oligonucleotide with the proviso that: the oligonucleotide comprises at least 8 residues; the oligonucleotide comprises at maximum twelve elements, which are capable of forming three hydrogen bonds each to cytosine bases; the oligonucleotide does not contain four or more consecutive elements, capable of forming three hydrogen bonds each with four consecutive cytosine bases (CCCC) within the target molecule or alternatively four or more consecutive elements of GGGG; the oligonucleotide does also not contain 2 or more series of three consecutive elements, capable of forming three hydrogen bonds each with three consecutive cytosine bases (CCC) within the target molecule, or alternatively 2 or more series of three consecutive elements of GGG; and the ratio between residues forming two hydrogen bonds per residue (2H–bond–R) with the target molecule and those residues forming three hydrogen bonds per residue (3H–bond–R) with the target molecule, is ruled by the following specifications: 3H–bond–R/3H–bond–R + 2H–bond–R ≥ 0.29; and synthesizing the oligonucleotide thus generated in a per se known manner.

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NOTIFICATION CONCERNING SUBMISSION OF PRIORITY DOCUMENTS

(PCT Administrative Instructions, Section 411)

To:

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P.O. Box 10 22 41
D-50462 Cologne
ALLEMAGNE

30 APR 1998

F 31.8.98/31.7.98

Date of mailing (day/month/year) 22 April 1998 (22.04.98)	
Applicant's or agent's file reference Me kk 980274wo	**IMPORTANT NOTIFICATION**

International application No.	**International filing date** (day/month/year)	**Priority date** (day/month/year)
PCT/EP98/00497	30 January 1998 (30.01.98)	31 January 1997 (31.01.97)

Applicant

BIOGNOSTIK GESELLSCHAFT FÜR BIOMOLEKULARE DIAGNOSTIK MBH et al

The applicant is hereby notified of the date of receipt by the International Bureau of the priority document(s) relating to the following application(s):

Priority application No:	Priority date:	Priority country:	Date of receipt of priority document:
97101531.8	31 Jan 1997 (31.01.97)	EP	15 Apr 1998 (15.04.98)

The International Bureau of WIPO
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Authorized officer

Yolaine CUSSAC

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From the INTERNATIONAL BUREAU

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NOTICE INFORMING THE APPLICANT OF THE COMMUNICATION OF THE INTERNATIONAL APPLICATION TO THE DESIGNATED OFFICES

(PCT Rule 47.1(c), first sentence)

To:
MEYERS, Hans-Wilhelm
P.O. Box 10 22 41
D-50462 Cologne
ALLEMAGNE

14 AUG 1998

31.8.98

Date of mailing (day/month/year) 06 August 1998 (06.08.98)	
Applicant's or agent's file reference Me kk 980274wo	**IMPORTANT NOTICE**
International application No. PCT/EP98/00497	**International filing date** (day/month/year) 30 January 1998 (30.01.98)
	Priority date (day/month/year) 31 January 1997 (31.01.97)
Applicant BIOGNOSTIK GESELLSCHAFT FÜR BIOMOLEKULARE DIAGNOSTIK MBH et al	

1. Notice is hereby given that the International Bureau has communicated, as provided in Article 20, the international application to the following designated Offices on the date indicated above as the date of mailing of this Notice:
   AU,BR,CA,CN,EP,IL,JP,KP,KR,NO,PL,US

   In accordance with Rule 47.1(c), third sentence, those Offices will accept the present Notice as conclusive evidence that the communication of the international application has duly taken place on the date of mailing indicated above and no copy of the international application is required to be furnished by the applicant to the designated Office(s).

2. The following designated Offices have waived the requirement for such a communication at this time:
   AL,AP,BA,BB,BG,CU,CZ,DE,EA,EE,GE,GW,HU,ID,IS,LC,LK,LR,LT,LV,MG,MK,MN,MX,NZ,OA,RO,
   SG,SI,SK,SL,TR,TT,UA,UZ,VN,YU

   The communication will be made to those Offices only upon their request. Furthermore, those Offices do not require the applicant to furnish a copy of the international application (Rule 49.1(a-bis)).

3. Enclosed with this Notice is a copy of the international application as published by the International Bureau on
   06 August 1998 (06.08.98) under No. WO 98/33904

REMINDER REGARDING CHAPTER II (Article 31(2)(a) and Rule 54.2)

If the applicant wishes to postpone entry into the national phase until 30 months (or later in some Offices) from the priority date, **a demand for international preliminary examination** must be filed with the competent International Preliminary Examining Authority before the expiration of 19 months from the priority date.

It is the applicant's sole responsibility to monitor the 19-month time limit.

Note that only an applicant who is a national or resident of a PCT Contracting State which is bound by Chapter II has the right to file a demand for international preliminary examination.

REMINDER REGARDING ENTRY INTO THE NATIONAL PHASE (Article 22 or 39(1))

If the applicant wishes to proceed with the international application in the **national phase**, he must, within 20 months or 30 months, or later in some Offices, perform the acts referred to therein before each designated or elected Office.

For further important information on the time limits and acts to be performed for entering the national phase, see the Annex to Form PCT/IB/301 (Notification of Receipt of Record Copy) and Volume II of the PCT Applicant's Guide.

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Authorized officer
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INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference	FOR FURTHER ACTION	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
980274wo Me/kk		
International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/EP98/00497	30/01/1998	31/01/1997
International Patent Classification (IPC) or national classification and IPC		
C12N15/11		
Applicant		
BIOGNOSTIK GESELLSCHAFT FÜR BIOMOLEKULARE...et al.		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 5 sheets, including this cover sheet.

   ☐ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of sheets.

3. This report contains indications relating to the following items:

   - I ☒ Basis of the report
   - II ☐ Priority
   - III ☐ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - IV ☒ Lack of unity of invention
   - V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations suporting such statement
   - VI ☐ Certain documents cited
   - VII ☐ Certain defects in the international application
   - VIII ☐ Certain observations on the international application

Date of submission of the demand	Date of completion of this report
20/08/1998	08.07.99
Name and mailing address of the international preliminary examining authority:	Authorized officer
European Patent Office D-80298 Munich Tel. (+49-89) 2399-0 Tx: 523656 epmu d Fax: (+49-89) 2399-4465	Grosskopf, R Telephone No. (+49-89) 2399

Form PCT/IPEA/409 (cover sheet) (January 1994)

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/EP98/00497

I. Basis of the report

1. This report has been drawn on the basis of (*substitute sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to the report since they do not contain amendments.*):

Description, pages:

1-28 as originally filed

Claims, No.:

1-17 as originally filed

Drawings, sheets:

1/36-36/36 as originally filed

2. The amendments have resulted in the cancellation of:

- ☐ the description, pages:
- ☐ the claims, Nos.:
- ☐ the drawings, sheets:

3. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)):

4. Additional observations, if necessary:

IV. Lack of unity of invention

1. In response to the invitation to restrict or pay additional fees the applicant has:

- ☐ restricted the claims.
- ☐ paid additional fees.
- ☐ paid additional fees under protest.
- ☐ neither restricted nor paid additional fees.

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/EP98/00497

2. ☒ This Authority found that the requirement of unity of invention is not complied and chose, according to Rule 68.1, not to invite the applicant to restrict or pay additional fees.

3. This Authority considers that the requirement of unity of invention in accordance with Rules 13.1, 13.2 and 13.3 is

☐ complied with.

☒ not complied with for the following reasons:

see separate sheet

4. Consequently, the following parts of the international application were the subject of international preliminary examination in establishing this report:

☐ all parts.

☒ the parts relating to claims Nos. 1-17(partially).

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	
	No:	Claims	1-17
Inventive step (IS)	Yes:	Claims	
	No:	Claims	1-17
Industrial applicability (IA)	Yes:	Claims	1-17
	No:	Claims	

2. Citations and explanations

see separate sheet

INTERNATIONAL PRELIMINARY EXAMINATION REPORT - SEPARATE SHEET

International application No. PCT/EP98/00497

Ad item IV:

This Authority agrees with the objection for lack of unity put forward by the search Authority.
The Applicant has paid one additional search fee and asked for an additional search of invention 39.01.
Consequently, also this Authority had to ask the Applicant to pay either an additional examination fee or to select one of the two groups searched.
However, taking into account the limited time period which is available for establishing the final report, this Authority will not insist on the payment of an additional examination fee, but will carry out an examination with regard to both groups.
This does, however, not mean that the lack of unity objection no longer applies.

Ad item V:

The following subject-matter has been searched and will, consequently, form the basis for this opinion:

(a) The method Claims 1 to 6
(b) the product claims insofar as they relate to the sequences of SEQ ID NO 41 and SEQ ID NO 519.

As far as the method claims are concerned and especially Claim 1, said method consists of two steps:

(i) the selection of a target sequence
(ii) the synthesis of an antisense oligonucleotide.

These two steps are "connected" by a rule which should be fulfilled by the resulting oligonucleotides. Said rule, however, has no consequences for the steps of preparing the oligonucleotides (otherwise one could also argue a method for preparing a compound having two C-atoms, i.e. the "rule" which must be fulfilled, is novel over a method for preparing acetic acid).
Thus, this rule has only relevance for the scope of the claim insofar as it has an

influence on the resulting products i.e. the oligonucleotides.
This means, however, if oligonucleotides which fall within the scope of said rule are known, the method for their preparation which consists merely of the two trivial steps mentioned above, could not be novel. Admittedly a method for preparing a known product may be novel, but merely if it comprises **steps** which do not form part of the prior art methods.
Since oligonucleotides are known which follow these rules (see e.g. D1; WO94/25588 but also several other documents cited in the search report), and said oligonucleotides are prepared by "selecting a target sequence" and "synthesising the oligonucleotide", at least Claims 1 and 2 are not novel.
The other features within Claims 3 to 6 (novelty provided, several of the alternatives mentioned in these claims would give rise to further objections for lack of unity) are routinely used as modifications during the preparation of antisense oligonucleotides (most of them also described in D1), and, thus, do not make any contribution to a possible inventive activity.

As far as the two products searched are concerned, they, strictly speaking, also lack novelty since they refer to sequences which "comprise" said sequences i.e. they encompass larger parts of the TGF-beta 1 and TGF-beta 2 gene.

But even if the claims were restricted to the specific fragments, an inventive activity could at best be acknowledged if said antisense oligonucleotides had some superior properties in comparison with antisense oligos which have been prepared or which could easily be prepared from the TGF genes, said oligos being even partially identical with these sequences (see e.g. SEQ ID NOs 57 and 136 of D1).
Such properties, however, have not been demonstrated e.g. by comparative tests.
Moreover, with regard to SEQ ID NO.: 519, it has to be mentioned that SEQ ID NO.: 57 of D1 is nearly **identical** (only one base shift). Thus, an inventive activity has to be denied in any case.